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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/575,181

01/30/2007

Ingrid Eileen Scheffer

1386/24

3488

25297

7590

06/10/2009

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EXAMINER

KAPUSHOC, STEPHEN THOMAS

ART UNIT

PAPER NUMBER

1634

MAIL DATE

DELIVERY MODE

06/10/2009

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/575,181	<b>Applicant(s)</b> SCHEFFER ET AL.	
	<b>Examiner</b> STEPHEN KAPUSHOC	<b>Art Unit</b> 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-27 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 April 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>06/16/2006; 05/25/2006</u> . | 6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u> .                 |

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
10575181	1/30/2007	SCHEFFER ET AL.	1386/24

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**EXAMINER**

STEPHEN KAPUSHOC

ART UNIT	PAPER
1634	20090527

DATE MAILED:

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner for Patents**

## **DETAILED ACTION**

Claims 1-27 are pending and examined on the merits.

### ***Information Disclosure Statement***

1. The listing of references in the specification is not a proper information disclosure statement. See pages 22-23 of the specification. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless these references have been cited by the examiner on form PTO-892, or provided by Applicants on an appropriate IDS (e.g. PTO-1449), they have not been considered.

### ***Objection to the Specification – Sequence Compliance***

2. This application (10/575,181) contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 at least for the reason(s) set forth below:

37 CFR 1.821(d) requires that :

Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

In the case of the instant Application, the sequences of primers are listed in Table 1 on page 21, however each recitation of a sequence is not accompanied by a sequence identifier.

In the instant case the table should be amended such that each sequence recitation is followed by the appropriate SEQ ID NO: from the sequence listing.

For example: ACAGGAAGTTAGGTGTGGTC (SEQ ID NO: 1).

**In order for any response to this Office Action to be considered fully responsive, the response must put the application in compliance with the sequence rules.**

***Claim Rejections - 35 USC § 112 2<sup>nd</sup> ¶ - Indefiniteness***

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 11-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are unclear over recitation of the phrase 'one of the assays', as recited in claims 11, 13, 14, 16-20 and 22-24, recitation of the phrase 'the sample DAN to be tested', as recited in claim 15, and recitation of the phrase 'said assay', as recited in claim 21. In each case there is not proper antecedent basis in the rejected claim or the claim from which the rejected claim depends for the unclear phrase. For example, claim 11 requires 'wherein one of the assays is a DNA hybridization assay', however

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there is no antecedent basis in claim 11 for any required assay, nor is there any basis for a required assay in claim 4 (from which claim 11 depends), or claim 1 (from which claim 4 depends).

### ***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-10, 17 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heron et al (2002) (citation #6 on the IDS of 5-25-2006).

Heron et al teaches several phenotypic parameters of BFIS, BFNS, and BFNIS diagnosis as well as aspects of mutations in particular genes that are related to BFNIS and BFNS. In particular the reference teaches a clinico-molecular correlation between missense mutations in the SCN2A gene and the BFNIS phenotype (p.851 – Abstract), and also that BFNS is frequently caused by mutations in the KCNQ2 and KCNQ3 genes (p.851, left col.).

Relevant to the limitations of claims 1-4, the reference provides that there is a clinico-molecular correlation between mutations in the SCN2A gene and the BFNIS phenotype, where in two family based studies missense mutations in the SCN2A cosegregate with the BFNIS phenotype in affected relatives of probands in two pedigree analyses (p.851 – Abstract; Figure 1).

Relevant to claims 5 and 6, the reference teaches analyses that include an SSCA assay and a sequencing assay, thus providing an assay to test for the presence of an alteration and assay to identify the nature of the alteration (p. 851, left col.).

Relevant to claim 7, the reference provides that BFNS is frequently caused by mutations in the KCNQ2 and KCNQ3 genes (p.851, left col.).

Relevant to claim 8, the reference teaches testing for the presence of alterations in the SCN2A gene and the KCNQ2 and KCNQ3 genes (e.g. p.851, right col.), as well teaching a clinico-molecular correlation between missense mutations in the SCN2A gene and the BFNIS phenotype (p.851 – Abstract), and also that BFNS is frequently

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caused by mutations in the KCNQ2 and KCNQ3 genes (p.851, left col.). The reference further provides diagnostic parameters (e.g. age of seizure onset) for BFNIS, BFIS, and BFNS.

Relevant to claims 9 and 10, the reference teaches analyses that include an SSCA assay and a sequencing assay, thus providing an assay to test for the presence of an alteration and assay to identify the nature of the alteration (p. 851, left col.).

Relevant to claim 17, the reference provides that individuals were screened with single-strand conformation analysis (SSCA) (p.851 – left col.), which is an SSCP assay.

Relevant to claim 24, the reference teaches the sequencing of exons to identify the nature of detected alterations (p.852 – left col.).

The teachings of Heron et al do not provide diagnostic methods per se. However, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have to have used the express teachings of Heron et al, particularly regarding the specific times of onset of seizures BFNS, BFIS, and BFNIS, the teachings regarding the clinico-molecular correlation between SCNA2 mutations and BFNIS, and the teaching that BFNS is frequently caused by KCNQ2 and KCNQ3 mutations, to develop methods of diagnosing a particular phenotype from among BFNS, BFIS, and BFNIS where SCN2A mutations are indicative of BFNIS and KCNQ2 and/or KCNQ3 mutations are indicative of BFNS, as required by the claims. One would have been motivated to create such diagnostic methodologies as the skilled artisan would recognize that using molecular analysis of genes associated with the particular



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conditions would allow more accurate diagnosis of distinct phenotypes with similar symptoms.

9. Claims 11, 12, 14-16, 18-23 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heron et al (2002) (citation #6 on the IDS of 5-25-2006), as applied to claims 1-10, 17 and 24 above, and further in view of Singh et al (2002) (US Patent 6,413,719).

Heron et al teaches several phenotypic parameters of BFIS, BFNS, and BFNIS diagnosis as well as aspects of mutations in particular genes that are related to BFNIS and BFNS. In particular the reference teaches a clinico-molecular correlation between missense mutations in the SCN2A gene and the BFNIS phenotype (p.851 – Abstract), and also that BFNS is frequently caused by mutations in the KCNQ2 and KCNQ3 genes (p.851, left col.).

Heron et al does not specifically provide for assays that include DNA hybridization (claim 11), probe hybridization to genomic DNA (claim 12), electrophoresis (claim 14), analysis of exon length (claims 15 and 26); DNA amplification with allele specific oligonucleotides (claim 16), RNase protection (claim 18), DGGE (claim 19), enzymatic assays (claim 20), MutS assays (claim 21), and assays which examine protein electrophoretic mobility and immunoassays (claims 22 and 23). However, such assay methods in the analysis of mutations were well known in the art at the time the invention was made, and are taught by Sing et al for the analysis of mutations in the KCNQ2 and KCNQ3 genes as associated with BFNS.

Relevant to the rejected claims, Singh et al provides for assays that include DNA hybridization (e.g.: Fig 1, relevant to claim 11), probe hybridization to genomic DNA (e.g.: Fig 1; col.11 Ins.35-40, relevant to claim 12), electrophoresis (e.g.: col.7 Ins.55-65; col.8 Ins.45-56, relevant to claim 14), DNA amplification with allele specific oligonucleotides (e.g.: col.11 Ins.35-40, relevant to claim 16), RNase protection (e.g.: col. 9 Ins.22-23, relevant to claim 18), DGGE (e.g.: col. 9 ln.22, relevant to claim 19), enzymatic assays (e.g.: col. 9 Ins.22-23, relevant to claim 20), MutS assays (e.g. col.9 Ins.3-5, relevant to claim 21), and assays which examine protein electrophoretic mobility and immunoassays (e.g.: col.11 Ins.1-19, relevant to claims 22 and 23).

With regard to claims 15 and 26, Singh et al teaches amplification of exons using primers complementary to flanking introns (e.g.: Fig 7; col 15 – Example 17; Table 4). Sing et al further teaches that gene mutations may comprise deletions that shorten the resulting protein (col.7 Ins.20-55; col.8 Ins. 29-35). Further relevant to the limitations of claim 26, it is noted that both Heron et al and Singh et al teach sequence analysis of genes to identify mutations.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the methods disclosed in Singh et al for the analysis and detection of alterations of genes associated with BFNS and BFNIS, as required by the claimed methods. The skilled artisan would have been motivated to use the methods as disclosed in Singh et al as the skilled artisan would recognize that such methods would provide alternative means for the analysis of gene alterations.

With regard to claims 15 and 26, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have analyzed the size of amplified SCN2A, KCNQ2 or KCNQ3 exons in a subject as compared known wild type exon lengths to detect exon alterations that are shorter in a subject exon and are thus indicative of a truncated encoded-protein. One would have been motivated to identify such alterations as both Heron et al and Singh et al indicate that loss of protein function may result in the pathological phenotype, where the skilled artisan would recognize, based on at least on the teachings of Singh et al, that gene deletion and protein truncation may result in loss of function.

10. Claims 13 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heron et al (2002) (citation #6 on the IDS of 5-25-2006), as applied to claims 1-10, 17 and 24 above, and further in view of Claes et al (2002) (US Patent 6,413,719).

Heron et al teaches several phenotypic parameters of BFIS, BFNS, and BFNIS diagnosis as well as aspects of mutations in particular genes that are related to BFNIS and BFNS. In particular the reference teaches a clinico-molecular correlation between missense mutations in the SCN2A gene and the BFNIS phenotype (p.851 – Abstract), and also that BFNS is frequently caused by mutations in the KCNQ2 and KCNQ3 genes (p.851, left col.).

Heron et al does not specifically provide for assays using high performance liquid chromatography (claim 13), or the specific comparisons used in the SSCA assay (relevant to claim 25). However, such assay methods in the analysis of mutations were

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well known in the art at the time the invention was made, and are taught by Claes et al for the analysis of mutations in the genes as associated with epilepsy.

Relevant to claims 13 and 25, Claes et al teaches amplification of subject gene exons (Table 1) and analysis of amplicon properties using high performance liquid chromatography (p.1328 – Mutation detection and molecular-genetic analysis). The methods of Claes et al comprise detecting aberrant DHPLC patterns of amplicons, and sequence analysis of exons with aberrant patterns.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the mutation detection and analysis methods of Claes et al for the detection and analysis of SCN2A mutations associated with BFNIS as taught by Heron et al. In a combination of such methods it would be obvious to compare the DHPLC patterns of amplicons of subject exons with the patterns of the same exons from non-mutant genes, where Heron et al provides that mutations in the SCN2A gene, as compared to wild-type gene sequences, are causative of BFNIS. One would have been motivated to use the particular methodologies rendered obvious by Heron et al in view of Claes et al based on the teachings of Heron et al that SSCA followed by sequence analysis is useful for mutation detection, and the successful application of the particular methodological techniques of Claes et al.

11. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Heron et al (2002) (citation #6 on the IDS of 5-25-2006), as applied to claims 1-10, 17 and 24 above, and further in view of Smtih et al (1996).

Heron et al teaches several phenotypic parameters of BFIS, BFNS, and BFNIS diagnosis as well as aspects of mutations in particular genes that are related to BFNIS and BFNS. In particular the reference teaches a clinico-molecular correlation between missense mutations in the SCN2A gene and the BFNIS phenotype (p.851 – Abstract), and also that BFNS is frequently caused by mutations in the KCNQ2 and KCNQ3 genes (p.851, left col.).

Heron et al does not specifically provide for assays comprising hybridizing amplified exon fragments from a subject with exons from non-mutant SCN2A gene. However, such methods for mutation detection were well known in the art at the time the invention was made.

Smith et al teaches methods for mutation detection wherein heterogeneous nucleic acids are hybridized, and non-complementary nucleic acids that from heteroduplexes are identified (e.g. p.4375 – Detection of mutations in PCR-amplified gene fragments).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used the mutation detection and analysis methods of Smith et al for the detection and analysis of SCN2A mutations associated with BFNIS as taught by Heron et al. In a combination of such methods it would be obvious to hybridize amplicons of subject exons with the amplicons of the same exons from non-mutant SCN2A genes, where Heron et al provides that mutations in the SCN2A gene, as compared to wild-type gene sequences, are causative of BFNIS. One would have been motivated to use the particular methodologies rendered obvious by Heron et al in

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view of Smith et al based on the teachings of Heron et al that mutation detection followed by sequence analysis is useful for mutation detection, and the teachings of Smith et al that methods comprising the detection of heteroduplexes are generally applicable for mutation screens (p.4379 – left col.)..

### ***Conclusion***

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/  
Art Unit 1634